Complete Summary

GUIDELINE TITLE

Acute lymphocytic/lymphoblastic leukemia.

BIBLIOGRAPHIC SOURCE(S)

Acute lymphocytic/lymphoblastic leukemia. Philadelphia (PA): Intracorp; 2005. Various p. [57 references]

GUIDELINE STATUS

This is the current release of the guideline.

All Intracorp guidelines are reviewed annually and updated as necessary, but no less frequently than every 2 years. This guideline is effective from April 1, 2005 to April 1, 2007.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Acute lymphocytic leukemia (ALL), also called lymphoblastic leukemia and acute lymphoid leukemia

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Treatment

CLINICAL SPECIALTY

Family Practice
Hematology
Internal Medicine
Oncology
Pediatrics

INTENDED USERS

Allied Health Personnel
Health Care Providers
Health Plans
Hospitals
Managed Care Organizations
Utilization Management

GUIDELINE OBJECTIVE(S)

To present recommendations for the diagnosis, treatment, and management of acute lymphocytic leukemia that will assist medical management leaders to make appropriate benefit coverage determinations

TARGET POPULATION

Individuals with acute lymphocytic leukemia

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis/Evaluation

1. Physical examination and assessment of signs and symptoms
2. Diagnostic tests:
    - Tissue analysis
    - Immunophenotyping (flow cytometry)
    - Blood work (complete blood count; hemoglobin, hematocrit, platelets; peripheral blood smear)

Treatment/Management

1. Chemotherapy including
    - Remission induction (vincristine; prednisone and anthracycline; cyclophosphamide with or without asparaginase)
    - Consolidation and maintenance therapy (cytarabine in combination with anthracycline or epipodophyllotoxin)
    - Prophylaxis and treatment of central nervous system involvement (intrathecal methotrexate)
    - Re-induction chemotherapy for relapsed acute lymphocytic leukemia (methotrexate with L-asparaginase or folinic acid rescue; cytarabine and teniposide; high-dose cytarabine combined with anthracycline, amsacrine, or other agents)
2. Stem-cell transplantation, including
    - Allogeneic transplant

    - Autologous transplant
    - Non-myeloablative transplant
3. Physical therapy
4. Referral to specialists
5. Case management strategies, including case initiation, case management focus, and discharge

MAJOR OUTCOMES CONSIDERED

- Effectiveness of treatment
    - Complete remission (CR) rates
    - Risk of relapse
    - Recurrence rates
    - Survival rates
- Side-effects, complications, and toxicities related to treatment

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Searches were performed of the following resources: reviews by independent medical technology assessment vendors (such as the Cochrane Library, HAYES); PubMed; MD Consult; the Centers for Disease Control and Prevention (CDC); the U.S. Food and Drug Administration (FDA); professional society position statements and recommended guidelines; peer reviewed medical and technology publications and journals; medical journals by specialty; National Library of Medicine; Agency for Healthcare Research and Quality; Centers for Medicare and Medicaid Services; and Federal and State Jurisdictional mandates.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Not Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not stated

METHODS USED TO ANALYZE THE EVIDENCE

Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Delphi)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

A draft Clinical Resource Tool (CRT or guideline) is prepared by a primary researcher and presented to the Medical Technology Assessment Committee or the Intracorp Guideline Quality Committee, dependent upon guideline product type.

The Medical Technology Assessment Committee is the governing body for the assessment of emerging and evolving technology. This Committee is comprised of a Medical Technology Assessment Medical Director, the Benefit and Coverage Medical Director, CIGNA Pharmacy, physicians from across the enterprise, the Clinical Resource Unit staff, Legal Department, Operations, and Quality. The Intracorp Guideline Quality Committee is similarly staffed by Senior and Associate Disability Medical Directors.

Revisions are suggested and considered. A vote is taken for acceptance or denial of the CRT.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Comparison with Guidelines from Other Groups
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Diagnostic Confirmation

Subjective Findings

- Average duration of complaints is 6 weeks
- Most signs and symptoms arise from anemia, thrombocytopenia, neutropenia:
    - Weakness
    - Lethargy/lassitude
    - Easy/excessive bruising
    - Shortness of breath
    - Headache
    - Nausea/vomiting

Objective Findings

- Clinical presentation indicates acute illness:
    - Muscular weakness
    - Pallor
    - Fever
    - Emesis
- Petechiae and ecchymoses
- Nosebleeds
- Lymphadenopathy (enlarged lymph nodes), hepato/splenomegaly may be present
- Bone tenderness
- Unintentional weight loss
- Anemia
- Thrombocytopenia
- Recurrent infection
- Pneumonia
- Sepsis
- Cellulitis

Diagnostic Tests

- Cytogenetic examination - morphology and cytochemistry
    - Tissue analysis to determine the number and shape of the chromosomes of the cells. This analysis plays a key role in diagnosis and treatment options and approaches as well as follow-up to treatment response.
- Immunophenotyping by flow cytometry to determine the cell morphology of disease. Antigens (proteins) on the cell surface and the antibodies produced by the body in response which match the antigen. This may be measured in:
    - Blood cells
    - Marrow cells or
    - Lymph node cells

Tissue typing helps provider determine the best treatment for the specific category of acute lymphocytic leukemia (ALL)

- Blood work
    - Complete blood count (CBC)

        - Bone-forming organ deficiencies, especially marrow depression, occur when lymphoblasts are present. Lymphoblast proliferation leads to anemia and thrombocytopenia (platelets <100,000 mm^3 [adults or children]).
        - Critical values: hemoglobin (Hgb) <9 gm/dL; hematocrit (Hct) <25 volume %; platelets (Plts) <30,000
    - Peripheral blood smear
        - In ALL, increased numbers of precursor cells occur (bands, neutrophils, and polynucleates ["polys"]).

Differential Diagnosis

- Other hematologic malignancies; distinguish from acute myelogenous leukemia (AML)
- Primary bone marrow failure
- Disorders with reactive lymphocytosis:
    - Infectious mononucleosis or Epstein-Barr
    - Cytomegalovirus (CMV) infections
    - Pertussis in children

Treatment Options

Chemotherapy

The treatment of ALL is divided into two phases: remission induction and post-remission (also called consolidation and maintenance) therapy. Induction chemotherapy is administered to produce a complete remission (CR) in the bone marrow. A patient is considered to be in remission when the bone marrow is normocellular with <5% blasts, there are no signs or symptoms of the disease, there are no signs of central nervous system (CNS) involvement, and the complete blood count, differential, platelet count, hematocrit, and hemoglobin are normal. The drugs commonly used for chemotherapy are vincristine; prednisone and anthracycline; and cyclophosphamide, with or without asparaginase. The drugs are given over a course of 4 to 6 weeks. Induction therapy results in a CR rate of 60 to 80% in adults. The rate at which a patient's disease enters CR correlates to treatment outcome.

Without additional treatment, approximately 90% of patients with ALL will have a recurrence in weeks or months. To prevent a recurrence, intensive post-remission therapy is given as soon as possible after recovery from induction therapy. Consolidation-therapy regimens usually include cytarabine (Ara-C) in combination with anthracycline or epipodophyllotoxin. Consolidation therapy generally continues for six months.

Maintenance therapy consists of weekly chemotherapy treatments continued for several years. Post-remission therapy can be accomplished with multiple intensive chemotherapy treatments given close together, or with a single high-dose chemotherapy treatment followed by stem-cell transplantation.

The prophylaxis and treatment of CNS involvement influence survival. CNS prophylaxis consists of chemotherapy (intrathecal or high-dose systemic) and possibly cranial irradiation. In patients with active CNS involvement, treatment

includes intrathecal methotrexate twice weekly until the cerebrospinal fluid (CSF) is cleared of lymphoblasts; thereafter, patients receive four weekly treatments and, subsequently, once-monthly injections of intrathecal methotrexate for one year. Treatment with intrathecal chemotherapy results in the lowest risk of relapse. With appropriate therapy, patients with CNS involvement have outcomes similar to those for patients without this complication.

Patients with relapsed ALL have an extremely poor prognosis, and allogeneic stem-cell transplant offers them the best chance for long-term, disease-free survival. Re-induction chemotherapy regimens include moderate-to-high-dose methotrexate with L-asparaginase or folinic acid rescue; cytarabine and teniposide; or high-dose cytarabine (HDAC) combined with an anthracycline, amsacrine, or other agents.

Stem-Cell Transplant

Stem-cell transplantation refers to transplantation of hematopoietic stem cells (HSC) from a donor into a patient. HSC are immature cells that can develop into any of the three types of blood cells (red cells, white cells, or platelets). HSC transplantation can be either autologous (using the patient's own stem cells) or allogeneic (using stem cells from a donor). HSC transplantation is provided to patients with hematological malignancies to rescue them from treatment-induced aplasia, after high-dose chemotherapy and/or radiotherapy has been administered to eliminate the cancer.

Many factors affect the outcome of a tissue transplant. The patient selection process is designed to obtain the best result for each patient.

Allogeneic Transplant

Allogeneic stem-cell transplantation involves using HSCs from a donor. In order for such a transplant to be successful, the donated cells must be similar, or a match, to the recipient's. Human leukocyte antigen (HLA) typing can identify donors who may be a perfect match. HLAs are proteins on the surface of cells. These proteins help the immune system identify a cell as either belonging to the body or from outside the body. There are three types each of class I and class II HLA. Increased survival is associated with a match between recipient and donor HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1.

Autologous Transplant

Autologous HSC transplantation is the transplantation of the recipient's own previously harvested stem cells. Autologous HSC transplant provides an alternative stem-cell source for patients who do not have an HLA-identical donor. It can also be performed in older patients, since the conditioning regimen for autologous transplantation is less toxic than the one for allogeneic HSC transplantation and does not create a graft-versus-host reaction. However, this lack of graft-versus-leukemia reaction with autologous HSC transplantation results in greater chances of disease relapse compared to the chances with allogeneic HSC transplantation. Contamination of autografts by malignant cells may account for the difference.

Non-Myeloablative Transplant

Non-myeloablative preparative regimens (also called mini-transplants) are designed to reduce regimen-related toxicities and allow allogeneic transplantation in patients who are older, have co-morbid conditions, or have toxicities from previous treatment. Non-myeloablative conditioning regimens fall into two categories: reduced intensity and minimally myelosuppressive. Conditioning regimen varies by study protocol and may include a purine analog, an alkylating agent, or low-dose total-body irradiation. The purine analogs (including fludarabine, cladribine, and pentostatin) are broadly cytotoxic, as well as immunosuppressive.

Source of Cells

HSCs are available in the peripheral blood, bone marrow, and umbilical cord.

Refer to related guideline for additional background and medical necessity information on stem cell transplantation for ALL.

Duration of Medical Treatment

- Medical - Optimal: 120 day(s), Maximal: 720 day(s)
    - Acute: Induction and consolidation phases can each last 4 to 8 weeks or more, depending on length of chemotherapy and severity of complications [e.g., cytopenia, exacerbation of comorbid condition(s)]
    - Maintenance therapy: usually provided for 2 years
    - A minority of patients need lifetime therapy.

Additional information regarding primary care visit schedules, referral options, specialty care, and physical therapy is provided in the original guideline document.

The original guideline document also provides a list of red flags that may affect disability duration, and return to work goals, including

- After hospitalization for chemotherapy
- Resolving complete blood count (HGH platelets) and hydration
- After HSC transplant

Note: Some patients with this condition may never return to work.

Case Management Directives (refer to the original guideline for detailed recommendations)

Case Initiation

Establish Case

- Document baseline information, history, key physical findings, patient's understanding, and safety factors.
- See Chemotherapy Chart in the original guideline document.

- The American Joint Committee on Cancer encourages use of the "TNM" classification system (T=primary tumor size; N=lymph node involvement; M=metastasis).
- Provide contact information for local and national support groups.

Coordinate Care

- Advocate for patient by managing utilization and charges.
- Document treatment plan.

Case Management Focus

Activity Deficit

- Document activity alteration as none, mild, moderate, severe, dependent, or bed-bound (based on most recent performance status) and interventions required.

Chemotherapy Intolerance

- Assess status, acute versus chronic, of toxic side effects on rapidly growing tissues, including bone marrow, epithelium, hair, sperm, and document intervention recommended.

Hemodynamic Instability

- Document bleeding complications, severity, and intervention recommended.

Immune Compromised

- Document establishment of protective isolation measures for a white blood cell count (WBC) less than 1,000/mm^3, implying dangerous susceptibly to infection.

Inadequate Nutrition

- Use optimal goal of remaining within 10% of pretreatment weight to document hydration and nutrition deficit as mild, moderate, severe, and response needed.

Mental and Emotional Alteration

- Ensure accurate diagnosis of any change in mental status.
- Document baseline or optimal mental and emotional functioning and their alterations due to cancer presence, comorbidity, surgery, or treatments.
- Assess and respond appropriately to the degree of debility caused by alterations listed in the original guideline document through benefit coordination or community resource activation.

Pain Control

- Document optimal pain management by characterizing severity and interventions undertaken to remedy or manage pain.

Oncologic Emergencies

- Document presence of or developing oncologic emergencies and report to attending physician, surgeon, or activate emergency medical technician (EMT) system as necessary.

Radiation Intolerance

- Document presence and severity of radiation side effects.
- Initiate early interventions for complications of radiation therapy.

Respiratory Instability

- Document respiratory deficit as mild, moderate, severe, and dependent, and respiratory rehabilitation enhancement measures.

Skin Integrity Deficit

- Document severity of skin integrity disruption.

Terminal Care

- Document optimal comfort measures and palliative care initiatives.

Discharge

Discharge from Case Management (CM)

- Document return to independence or stabilized functional status and closing conversations with patient, caregiver, physician, pharmacist, and care providers.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is not specifically stated for each recommendation.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

General Potential Benefits

Appropriate diagnosis, treatment, and management of acute lymphocytic leukemia to assist medical management leaders in making appropriate benefit coverage determinations

Specific Benefits

- Prophylaxis and treatment of central nervous system (CNS) involvement influence survival. With appropriate therapy, patients with CNS involvement have outcomes similar to those for patients without this complication.
- The conditioning regimen for autologous transplantation is less toxic than the one for allogeneic hematopoietic stem cells (HSC) transplantation and does not create a graft-versus-host reaction.
- Induction therapy results in a complete remission (CR) rate of 60-80% in adults.
- Treatment with intrathecal chemotherapy results in the lowest risk of relapse.
- Patients with relapsed acute lymphocytic leukemia (ALL) have an extremely poor prognosis, and allogeneic stem-cell transplant offers them the best chance for long-term, disease-free survival.

POTENTIAL HARMS

Refer to the Case Management Focus section of the "Major Recommendations" field for information on potential complications and strategies to address them, or refer to the original guideline document.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Acute lymphocytic/lymphoblastic leukemia. Philadelphia (PA): Intracorp; 2005. Various p. [57 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1997 (revised 2005)

GUIDELINE DEVELOPER(S)

Intracorp - Public For Profit Organization

SOURCE(S) OF FUNDING

Intracorp

GUIDELINE COMMITTEE

CIGNA Clinical Resources Unit (CRU)
Intracorp Disability Clinical Advisory Team (DCAT)
Medical Technology Assessment Committee (MTAC)
Intracorp Guideline Quality Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Not stated

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

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GUIDELINE AVAILABILITY

Electronic copies: Intracorp guidelines are available for a licensing fee via a password protected, secure Web site at www.intracorp.com.

Reprints of complete guideline content may be purchased for $35.00 per title (plus tax in TX at 8.25% and CT at 1.0%). Please send e-mail request to lbowman@mail.intracorp.com.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Policies and procedures. Medical Technology Assessment Committee Review Process. Philadelphia (PA): Intracorp; 2004. 4 p.
- Online guideline user trial. Register for Claims Toolbox access at www.intracorp.com.

Licensing information and pricing: Available from Intracorp, 1601 Chestnut Street, TL-09C, Philadelphia, PA 19192; e-mail: lbowman@mail.intracorp.com.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on May 23, 2005. The information was verified by the guideline developer on June 7, 2005.

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Date Modified: 10/9/2006